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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,859	02/26/2002	Joseph Altin	EM436365176US	8566

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EXAMINER	
POPA, ILEANA	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 09/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/031,859	ALTIN ET AL.	
	Examiner	Art Unit	
	Ileana Popa	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,5,7,8 and 10-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,5,7,8 and 10-39* is/are rejected.

7)☒ Claim(s) *8 and 39* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of the invention of Group II in the reply filed on 07/03/2006 is acknowledged. Upon considering the Applicant's arguments, together with the fact that examining all claims together does not pose a burden, the Examiner is withdrawing the requirement for restriction.

Claims 3, 6, and 9 have been cancelled.

Claims 1, 2, 4, 5, 7, 8, and 10-39 are pending and under examination

Claim Objections

2. Claim 8 is objected to because of the following informalities: claim 8 recites the limitation of "wherein the metal chelating group is nitriloacetic". The correct terminology is nitriloacetic acid. Appropriate correction is required.

3. Claim 39 is objected to because of the recitation of "DTDA". Abbreviations, unless otherwise obvious and /or commonly used in the art, should not be recited in the claims without at least once reciting the entire phrase for which the abbreviation is used. Appropriate correction is required.

Claim Rejections - 35 USC § 112, 2nd paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

5. Claims 24 (to the extent that it reads on any biological response and the

treatment of any disease), 31-34, 35 (to the extent that it reads on a disease), and 36, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 24 and 31-36 reciting " modifying any biological response or for the treatment of any disease" and "a method of treatment" are not clear. Without a clear indication of the pathophysiological state to be treated or of the biological response to be modified, the metes and bounds of the claim cannot be determined and the claim is indefinite. Amending the claim by specifying the pathophysiological state to be treated would obviate this rejection. However, Applicants are advised that amending the claims to specify the pathophysiological state to be treated would raise new issues under 35 U.S.C. 112, first paragraph, enablement.

6. Claims 4, 5, and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 4, 5, and 8 are indefinite because they are dependent on the cancelled claim 3.

7. Claims 1 and 30 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since

the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949).

In the present instance, claim 1 recites the broad limitation of "amphiphilic molecule" followed by the narrow limitation of "lipid". Claim 30 recites the narrow limitation of "membranous structure" and the claim also recites "cells", which is the a broader statement of the range/limitation. Moreover, it is not clear how a narrow limitation (i.e., the membranous structure) can comprise a broader limitation (i.e., cells), as recited.

8. Claim 35 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 35, reciting "to enhance immunity to a specific tumor or disease" is not clear. While methods to enhanced immunity toward disease-causing pathogens are

widely used in the art, it is not clear how to enhance immunity towards a disease. Therefore, the metes and bounds of the claim cannot be determined and the claim is indefinite.

9. Claims 27-30 and 39 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationship is: the presence of a polypeptide tag in the molecule to be engrafted. Since claims 27-30 and 39 do not recite such a polypeptide tag, it is not clear what the purpose of incorporating a chelator lipid (i.e., the presence of a chelator group) is.

10. Claim 18 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 18 is indefinite in its use of the words "engrafted or anchored". The specification states that the terms are interchangeable. Therefore, it is confusing why they are recited in alternative. If they are intended to mean the same thing, then the use of both terms is redundant.

11. Claim 18 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim Rejections - 35 USC § 112 – written description

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1, 2, 7, 8, and 10-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description Requirement" makes it clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosures of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol.

66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3rd column).

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that the Artisan can reasonably conclude the inventors had possession of the claimed invention. Such possession may be demonstrated by describing the claimed invention with all its limitations using such descriptive means as words, structures, figures, diagrams, and/or formulae that fully set forth the claimed invention. Possession may be shown by an actual reduction to practice, showing that the invention was "ready for patenting", or by describing distinguishing identifying characteristics sufficient to show that the Applicants were in possession of the claimed invention (January 5, 2001, Fed. Reg., Vol. 66, No. 4, pp.1099-11).

In analyzing whether the written description requirement is met for the genus claims, it is determined whether representative numbers of species have been described by their complete structure and functional characteristics.

Claims 1, 2, 7, 8, and 10-30 encompass a variety of polypeptide tags and chelating groups. Therefore, claims 1, 2, 7, 8, and 10-30 encompass wide and variable genera of polypeptides and chelating groups the structure of which is not sufficiently disclosed in the specification and the claims.

When the claim is analyzed in light of the specification, the polypeptide can be any polypeptide as long as it binds to a chelating group (p. 3, lines 8-20).

However, apart from the exemplification of histidine tag and nitriloacetic acid (NTA) as its corresponding chelating group, the instant specification fails to teach any other polypeptide tag or chelating group. The instant specification fails to provide a representative number of species for the broad genera of a polypeptide tag or chelating group. The genus of the polypeptide tag is described by its ability to bind chelating groups and the genus of chelating groups is described by its ability to bind polypeptide tags, but the specification does not provide any disclosure as to what would have been the complete structure of sufficient number of species of the claimed genera. Additionally, the specification does not describe what would have been the identifying characteristics, such as specific features and functional attributes, of the different polypeptide tags or chelating groups. Thus, it is apparent that at the filing date of the present application, Applicants did not have in possession a representative number of species for the broad genera of a polypeptide tags or chelating groups. The claimed invention as a whole is not adequately described if the claims require essential or critical elements that are not adequately described in the specification. A skilled artisan cannot fully envision the detailed structure of the broad genera of polypeptide tags or chelating groups, as claimed. In conclusion, this limited information is not sufficient to reasonably convey to one of ordinary skills in the art that the Applicants invented what was claimed. Consequently, the Applicants were not in possession of the instant claimed invention, at the time the application was filed.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

15. Claims 1, 2, 7, and 10-15 are rejected under 35 U.S.C. 102(e) as being anticipated by Stewart et al. (U.S. Patent No. 6,087,452).

Stewart et al. teach a method of modifying micelles (i.e., liposomes) by incorporating an NTA-surfactant into the micelles, followed by interaction with a protein molecule to be engrafted, wherein the protein molecule has a covalently attached polypeptide tag comprising six histidine residues and wherein the micelles thus formed may be used for drug delivery (column 2, lines 28-62, column 3, lines 5-10, 36-45, 66, and 67). Stewart et al. teach interaction of the micelles with ligands specific for the engrafted protein (i.e., the chelator groups are oriented toward the outside surface of the micelles) (column 2, lines 63-66). Since they also teach using these micelles for drug delivery, the limitation of their interaction with a ligand molecule expressed on a particular cell type is an inherent property of the micelles of Stewart et al. With respect to the limitation of the surfactant having a hydrophilic head and one or more hydrophobic tails (claim 10), this is inherent to surfactants. With respect to the limitation recited in claim 7, it would have been obvious to the ordinary skilled artisan to form the

micelles by sonication or extrusion/filtration, since these are routine laboratory procedures. Since Stewart et al. teach all the limitation of the instant claims, the claimed invention is anticipated by the above-cited art.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claims 1, 2, 4, 5, 7, 8, 11-17, 20-30, and 37-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sevaraj et al. (U.S. Patent No. 6,491,925), in view of Dorn et al. (Biol Chem, 1998, 379: 1151-1159).

** Claims 4, 5, and 8 are included in the instant rejection to the extent that they are drawn to a method of modifying a biological or synthetic membrane for the purpose of altering immunity or targeting of drugs/agents to a specific site when administered *in vivo*.

Sevaraj et al. teach a method of modifying tumor cell membranes or isolated tumor cell membranes by incorporating a fusion protein consisting of the extracellular domain of B7.1 in combination with a glycosylphospatidylinositol (GPI) anchor, wherein the composition further comprises an antigen suitable for stimulating cellular immunity and activating a cytotoxic response when administered *in vivo* (claims 1, 2, 7, 16, 17, 21-24, 27, 28, and 37-39, Examples 9 and 10) (column 2, lines 31-67, column 3, lines 1-

50, column 18, lines 56-60, column 19, lines 29-59). Sevaraj et al. teach that membrane-incorporated GPI-anchored B7.1 is able to deliver a co-stimulatory signal to T cells *in vivo* (i.e., the engrafted molecule is capable of interacting with a specific type of cell, as recited in claims 4 and 20, the engrafted molecule is a receptor domain, as recited in claims 5, 25, 26, and 29, the engrafted molecule is a co-stimulatory molecule, as recited in claim 38, or the membranous structure is targeted to a particular cell within the body, as recited in claim 30) (column 20, lines 17-20). Sevaraj et al. do not teach engrafting molecules by using chelator lipids that bind the histidine tag of the molecule to be engrafted. Dorn et al. teach reversible and oriented immobilization of proteins into chelated lipid bilayers (i.e., membranes with incorporated chelator lipids), wherein the chelator group is NTA and wherein the proteins are engineered to comprise a polypeptide tag of five to six histidine residues (claims 8 and 11-15) (p. 1151, column 2, second and third paragraphs, p. 1152, columns 1 and 2, p. 1153, column 1). Dorn et al. teach teach that, due to the engineered histidine tag, the orientation of the proteins in the chelator membranes can be controlled (claims 1 and 2) (p. 1156, column 2, last paragraph). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the tumor cell membranes of Sevaraj et al. by using the method of Dorn et al., with a reasonable expectation of success. The motivation to do so is provided by Dorn et al., who teach that immobilization via chelator lipids as being useful for the immobilization of proteins at many different interfaces whereby the function of the protein is preserved since the method allows for the controlled orientation of the proteins in the membranes (p. 1156, column 1 bridging column 2). One of skill in

the art would have been expected to have a reasonable expectation of success because the art teaches the successful us of chelator lipids for the engraftment of molecules into a variety of membranes. With respect to the limitation recited in claims 7, 16, 2127, 30, and 39, it would have been obvious to the ordinary skilled artisan to form the liposomes by sonication or extrusion/filtration, to use the washing steps when incorporating chelator lipids and proteins into the membranes or to suspending the membranes in a solution appropriate for the *in vivo* administration, since these are routine laboratory procedures. With respect to the limitation of using liposomes (claims 7, 18-20) or of the limitation of NTA-DTDA (claim 39), it would have been obvious to one of skill in the art to use liposomes or different chelator lipids such as NTA-DTDA according to the needs. The following is a citation from MPEP:

2144 Sources of Rationale Supporting a Rejection Under 35 U.S.C. 103

RATIONALE MAY BE IN A REFERENCE, OR REASONED FROM COMMON KNOWLEDGE IN THE ART, SCIENTIFIC PRINCIPLES, ART-RECOGNIZED EQUIVALENTS, OR LEGAL PRECEDENT

The rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). See also In re Kotzab, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000) (setting forth test for implicit teachings); In re Eli Lilly & Co., 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990) (discussion of reliance on legal precedent); In re Nilssen, 851 F.2d 1401, 1403, 7 USPQ2d 1500, 1502 (Fed. Cir. 1988) (references do not have to explicitly suggest combining teachings); Ex parte Clapp, 227 USPQ 972 (Bd. Pat. App. & Inter. 1985) (examiner must present convincing line of reasoning supporting rejection); and Ex parte Levengood, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993) (reliance on logic and sound scientific reasoning)

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

18. Claims 1, 2, 4, 5, 7, 8, 10-30, and 37-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sevaraj et al. taken with Dorn et al., as applied to claims 1, 2, 4, 5, 7, 8, 11-17, 20-30, and 37-39 above, in further view of Stewart et al.

Sevaraj et al. taken with Dorn et al. do not teach chelating surfactants. Stewart et al. teach controlled immobilization of active proteins bearing a polyhistidine tag on micelles containing an NTA-surfactant (column 2, lines 28-62, column 3, lines 5-10 and 36-45). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method taught by Sevaraj et al. taken with Dorn et al. by replacing the chelator lipid with a chelator surfactant, with a reasonable expectation of success. The motivation to do so is provided by Stewart et al., who teach their surfactants as useful for *in vivo* application since they are biocompatible and have low immunogenic activity and toxicity (column 3, lines 42-45). One of skill in the art would have been expected to have a reasonable expectation of success in making such a composition because the art teaches that such composition can be successfully made.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

19. Claims 1, 2, 4, 5, 7, 8, 11-30, and 37-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sevaraj et al. taken with Dorn et al., as applied to claims 1, 2,

4, 5, 7, 8, 11-17, 20-30, and 37-39, in further view of both Olson et al. (Int J Cancer, 1997, 73: 865-870) and Battegay (J Mol Med, 1995, 73: 333-346, Abstract).

Sevaraj et al. taken with Dorn et al. do not teach VEGF or VEGF together with a cytotoxic agent incorporated by the liposomes (claims 18 and 19). Olson et al. teach VEGF-diphteria toxin conjugate as a vascular targeting agent that is toxic for endothelial cells and inhibits neovascularization and tumor growth, wherein VEGF functions to target the toxin to the neovasculature (Abstract, p. 866, columns 1 and 2). Olson et al. do not teach liposomes incorporating a cytotoxic agent. Battegay teaches that natural or synthetic angiogenesis inhibitors such as angiostatin or thalidomide are used to inhibit the formation of blood vessels required for tumor growth. It would have been obvious to one of skill in the art, at the time the invention was made, to use liposomes with engrafted VEGF (for targeting of the liposomes to the neovessels) and engrafted angiostatin or incorporated thalidomide (for inhibiting the growth of neovessels), with a reasonable expectation of success. The motivation to do engraft VEGF is provided by Olson et al., who teach that VEGF can be used to target cytotoxic agents to the endothelail cells of the neovessels. The motivation to engraft angiostatin/incorporate thalidomide is provided by Battegay who teach these agents as useful to inhibit tumor growth by inhibiting the growth of tumor neovasculature. One of skill in the art would have been expected to have a reasonable expectation of success in making and using such a composition because the art teaches that such com[positions can be successfully made and used. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

20. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ileana Popa, PhD

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PRIMARY EXAMINER